Improvement steady, so that he considered himself cured and finally discontinued visits. The psoriasis, too, paled away and disappeared, except for a few scales here and there.

CASE X.—Mr. B., aged sixty years; druggist. Complained for years of severe flatulence and almost constant tenesmus, with passages of small quantities of mucus and thin fermentative material; very nervous, wornout, dizzy; sallow complexion. Also nails coursely ridged, extensively undermined and hanging on merely by the roots. Received lavage twelve times in one month; cut out all fermentative food. Improvement immediate, with eventual cure. The nails, too, showed an unexpected and rapid improvement, growing up on a rosy, healthy looking base.

COMPARATIVE STUDY OF THE TOXIC EFFECTS OF THE NATURAL AND SYNTHETIC SALICYLIC ACIDS.

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THE task which we originally proposed to ourselves in designing this series of experiments was that we should try to determine the toxic and fatal doses of the natural and synthetic acids and their salts. It was intended to present a brief view of this problem, molded by the inherent constitution of the two drugs. The clinical matter was dealt with only so far as it seemed to throw light on the relation of chemical structure to therapeutic or toxic effects; but it has been found necessary to make greater use of clinical observations, and to treat the whole subject in an evolutionary manner. We will begin with a brief statement of the theme.

Salicylic acid prepared from oil of wintergreen is slightly milder than salicylic acid prepared in other ways. This fact was noticed by Stokvis in 1896, but the discrepancy has remained unexplained, and, indeed, practically undiscussed by chemists and physiologists of late years.

In order to institute a comparison we have examined the acids and their sodium salts, which are to be easily procured, and we have made some clinical studies of the action of the following substances which may be described as complementary: Cinnamate of sodium, phthalic acid, saligenin, salicin, methyl salicylate. The principle recently elaborated by Zadek, who adopted it from Stricker, is one which we have followed. This principle is that salicylic acid is

the ultimate result of any reaction in the body in which these allied substances are concerned.

Comparisons between the two have been instituted by pharmacologists. Studies of this nature have been published by Waddell, Hewlett, Eggleston, and Hunzlik. Intelligent review of these papers is not easy; in much they may be sound, but a strong bias is manifest in all of them.

The dispute over the virtues of natural and synethetic salicylic acids has always been confined to America, and its consequences remain, so far as truth and science are concerned, in an undoubted exacerbation of medical jealousy and a rapid growth of prejudice and ignorance. European writers have not disputed over a subject which is, or ought to be, purely scientific. Probably they have not thought it worth while.

Stokvis gives a fair summary of the science. We have found it accurate, the only point of difference being that salicylic acid is today manufactured with more skill than it was in 1896. But whether the samples which are sold are still free from the injurious cresols and the therapeutically useless parahydroxy benzoic acid is a matter of doubt.

The specimens examined by Stokvis were analyzed by Van't Hoff, and were presumably pure. He tried three acids: one prepared from oil of gaultheria, one prepared from anthranilic acid, and one prepared from phenol. They were similar in all respects. As our results have agreed with those of Stokvis, we tested our samples in the same way.

Fischer states[1] that pure natural salicylic acid melts at 156.8° C., while commercial acid melts at 153.5° C.

According to Bloch,[2] even a small proportion of creosotic acid lowers the melting-point of natural and synthetic salicylic acids. We found:

Purity of the salicylic acids used as determined by titration with $\frac{N}{10}$ KOH: Natural, 98 per cent.; synthetic, 98.54 per cent. These acids were recrystallized three times from hot water and melting-points taken of each crystallization as follows:

	Natural.	Synthetic.
Original acid	156.2° to 157.8°	155.9° to 157.1°
First recrystallization	156.2° to 157.7°	156.2° to 157.5°
Second recrystallization	156.8° to 157.8°	156.8° to 158.0°
Third recrystallization	156.8° to 158.0°	156.8° to 158.0°

Salicylic acid does not melt sharply. The temperatures given here are the points where (1) the acid fuses sufficiently to flow, and (2) fusion is complete. According to Smith[3] the melting-point of the synthetic acid is 158.5.

[1] Pharm. Zentralbl., xlii, S. 327.
[2] Pharm. Jour., 1890, lxxii, 429.
[3] Ibid., 1915, p. 617.

The original acids were sublimed, sublimates being taken at intervals. The recrystallized acids (third recrystallation) were also sublimed. Their melting-points were as follows:

	Natural	Synthetic.
First sublimate	155.8° to 157.0°	156.0° to 156.8°
Second sublimate	156.0° to 156.8°	156.0° to 156.8°
Recrystallized	156.0° to 156.9°	156.0° to 156.7°

The lower melting-points of the sublimed acids are no doubt due to a slight decomposition into phenol, the presence of which tends to lower the melting-point.

Solutions of sodium salicylate (25 per cent.) were prepared by dissolving the acids, together with sodium bicarbonate, in molecular proportions as follows:

Salicylic acid, natural (98 per cent.)	22.0050
Sodium bicarbonate (99.7 per cent.)	13.1621
Water q. s. to make	100.0 c.c.
Salicylic acid, synthetic (98.64 per cent.)	21.8622
Sodium bicarbonate (99.7 per cent.)	13.1624
Water q. s. to make	100.0 c.c.

Sodium salicylate, natural (25 per cent.).
Sodium salicylate, synthetic (25 per cent.).

Specific gravity at 20° C.	1.10276	1.10275
Optical rotation	0°	0°

It may, therefore, be concluded that we are dealing with the same chemical structures. The following is a summary of Stokvis's papers:

Charteris and Macleman showed a considerable difference between the acid prepared from oil of gaultheria and the synthetic acid. The results led both authors to the conclusion that the artificial acid, in spite of chemical purity, for no cresols were found, must be ranked as a physiologically impure substance. In comparing salicylic acids made from phenol with that prepared in other ways, we, of course, included the natural acid. As the interest of the subject is chiefly theoretical, we instituted our comparison by the experimental method. The phenol salicylic acids used, the anthranilic acid, and the acid prepared from oil of gaultheria are chemically the same. Solubility, elementary analysis, and polarization as tested in the laboratory of Van't Hoff, gave the same results. The molecular arrangement of three acids was identical, which would imply physiological identity. But in the animal experiment the case was different.

Sodium salicylate was used in all experiments. They fell into three parts: excretion and changes in the urine, the toxic and lethal doses, the physiological action in men.

The acid prepared from oil of gaultheria manifested a more rapid rate of excretion.

The cause of this quicker excretion is twofold: The natural acid is less active than the others. In rabbits, clear signs of poisoning appeared after large doses, 700 to 800 mg., the fatal dose being 1300 to 1400 mg. per kilogram of the animal's weight. Toxic effects were manifested by profound disturbance of the central nervous system and respiration, paralysis of the hind legs, dyspnea, stupor. Of great interest is the fact that the acid prepared from oil of gaultheria produced almost no tremor, which, however, in the case of the other acids, appeared constantly after doses of 700 to 900 mg., together with convulsions. These toxic symptoms were entirely wanting to the action of the gaultheria acid. Given the same animal and the same doses there was less disorder after the natural acid. The fatal dose, however, of the three acids was nearly the same.

As an extension of these researches, Dr. Morel undertook some on himself. The effects on pulse, temperature, appetite, and other functions were less marked in the case of the acid prepared from gaultheria. The rate of breathing was constantly raised by the phenol and anthranilic acids, but the natural acid caused virtually no change in the respiration.

It appears from these researches that the quantitative difference between the acids is so clearly demonstrated that we must agree wholly with the conclusion of Charteris and Maclennan when they pronounce the natural acid less toxic. To explain this difference, one must consider the greater ratio of excretion of the natural acid, which is due to the greater osmotic properties.

This is not only a sufficiently complete account, for practical purposes, of the systematic side of the subject, but is full of precisely that relation of the living organism to the chemical structure of the drug employed which can be treated properly only by a writer who knows chemistry and physiology, but has a great practical knowledge of the difference between the animals themselves. Rabbits and guinea-pigs are less sensitive than dogs, and dogs less sensitive than men, while human beings in health and disease show marked variations of physiological response to the salicylates.

In the following experiments we began with the intravenous method of injection, next we undertook subcutaneous injection, and lastly administration by the stomach tube. Clinical observations extending over many years are introduced, but in the form of a summary, as it would be impossible to report them in detail. They are introduced merely for the purpose of throwing light on the toxic and fatal doses of the various salicylates.

Injections of sodium salicylate under the skin are very painful, while it is most difficult to inject solutions of the salicylic acids into the veins. It was found that alcoholic solutions caused necrosis at

the point of the injection into the ear vein of rabbits. In intravenous injection the formula cited by Hasenfeld is the best:

Sodium salicylate	8.0
Caffeine sod. salicylate	2.0
Water or saline	50.0

Dissolve and filter.

The injections were begun in April, 1915, and continued to June, 1916, in four series of animals. In human cases, injections were begun several years ago, men being already reported.

INTRAVENOUS INJECTIONS. Second series: In testing the effects and comparative lethal doses of synthetic and natural sodium salicylate, 8 rabbits, averaging 3½ pounds each, were used—4 for the synthetic and 4 for the natural salts.

Intravenous injections were given, using the marginal ear veins, beginning with 200 mg. and increasing 100 mg. at a time until 800 mg. was reached.

Practically no symptoms developed from either the synthetic or natural salts, and it was impossible to see any difference between the two salts. Rabbits injected with 800 mg. of either the synthetic or natural salts died almost immediately after receiving the injection.

These injections were given twenty-four hours apart to permit the rabbits to eliminate the salts and to recover from the shock of the previous injections.

The only obvious symptoms of these injections short of the lethal dose was a rapid necrosis of the ears of the rabbits injected.

CONCLUSION. There is, in rabbits, no very obvious difference in the toxic action between synthetic and natural sodium salicylate when injected intravenously.

SUBCUTANEOUS INJECTIONS. Subcutaneous injections of synthetic and natural sodium salicylate failed to show any difference in toxicity. As these injections were very painful to the rabbits they were not carried beyond 800 mg., which was not lethal, and in fact produced no symptoms excepting those of extreme pain at the sight of injections, which subsided in from five to ten minutes.

Administered through Stomach Tube. The rabbits averaging 3½ pounds in weight were given respectively 1.5 gms. of natural and synthetic sodium salicylate dissolved in distilled water, administered through stomach tube, the stomachs of both animals being empty. The only symptoms of the above amounts were that rabbits were very quiet for an hour and a half, after which period they ate carrots with normal relish. At frequent intervals the animals were made to move about their cages, but no signs of paralysis were observed.

This treatment was continued at twenty-four-hour intervals, increasing each dose by 1.5 gm. (without any symptoms with the exception that the rabbits waited, before eating, for longer and

longer periods of time after treatment). Following the introduction of 6 gms. of the natural and synthetic salts, both rabbits showed symptoms of distress, and shortly became paralyzed. The rabbit that had been given the synthetic salt showed constantly increasing severity of symptoms, and finally became completely paralyzed, and died seven hours after receiving 6 gms. of the synthetic salt.

The rabbit that received the 6 gms. of the natural salt showed immediate symptoms of distress and became partially paralyzed, but those symptoms gradually subsided, and the following morning the animal ate carrots and bread without difficulty, and with seeming relish. This rabbit lived about two weeks and seemed to be normal in every way, but it died suddenly just after eating carrots. Autopsy failed to show any stomach lesions, but the liver showed extensive coccidiosis infection.

The synthetic rabbit, on autopsy, showed no inflamed stomach distended with fecal matter; other organs seemed to be macroscopically normal.

Second Pair of Rabbits Given Salts by Stomach. The above test was repeated with two rabbits weighing 4 pounds each. One rabbit received 5 gms. of natural sodium salicylate and the other one received 5 gms. of synthetic sodium salicylate, dissolved in 10 c.c. of distilled water and made up to 40 c.c. when administered by stomach tube. Both showed slight signs of distress in a few moments, but soon settled down quietly in their cages, neither showing any inclination to eat or drink. The natural rabbit died in three and a half hours without having developed any marked symptoms or signs of paralysis.

The rabbit that received the synthetic salt died some time during the night, but at the time of the death of the rabbit that received the natural salt the rabbit that had received the synthetic salt, while he would not eat, seemed in very good condition.

Postmortems of both of the above animals showed badly inflamed stomachs that were very much distended and filled with fecal matter.

Third Pair of Rabbits Given Salts by Stomach. These rabbits weighed 3¼ and 4 pounds. The 3¼-pound rabbit was given 4 gms. of the natural salt and the 4-pound rabbit was given 4 gms. of the synthetic salt. Both animals, like previous ones, became very quiet in a few moments and refused to move about their cages unless forced to, neither, however, showing any signs of paralysis.

In three hours and a half after ingesting the salt the natural rabbit was suddenly seized with a convulsion and died in a few moments. Postmortem showed a badly inflamed stomach distended with fecal matter.

The synthetic rabbit, however, drank freely of water and ate a carrot about four hours after ingesting the salt, and is still alive and eats well, but shows marked disinclination to move about.

CHART I.

	Dose given intravenously.	Date.	Temperature at time of injection.	Time of injection.	Temperature readings at five-minute intervals after injection.									
					5 min.	10 min.	15 min.	20 min.	25 min.	30 min.	35 min.	40 min.	45 min.	50 min.
		1915												
Natural salt	200 mg.	June 17	37.0° C.	2.40 P.M.	37.4° C.	38.0° C.	38.0° C.	36.6° C.	35.0° C.	36.0° C.	37.0° C.	37° C.	37° C.	
Synthetic salt	200 mg.	June 19	37.6° C.	10.45 A.M.	38.0° C.	38.0° C.	38.0° C.	37.5° C.	37.0° C.	37.0° C.	36.8° C.	37° C.	37° C.	37° C.
Synthetic salt	200 mg.	June 22	36.8° C.	5.45 P.M.	38.0° C.	37.4° C.	38.0° C.	37.4° C.	37.0° C.	37.0° C.	37.0° C.	37° C.	37° C.	37° C.
Natural salt	200 mg.	June 24	37.2° C.	11.40 A.M.	38.2° C.	38.0° C.	37.8° C.	37.8° C.	37.5° C.	37.2° C.	37.0° C.	37° C.	37° C.	37° C.

Weight of rabbits, 2¼ pounds; same rabbit for both tests.

CHART II.

	Dose given intravenously.	Date.	Temperature at time of injection.	Time of injection.	Temperature readings at five-minute intervals after injection.									
					5 min.	10 min.	15 min.	20 min.	25 min.	30 min.	35 min.	40 min.	45 min.	50 min.
		1916												
Natural salt	200 mg.	June 17	37° C.	2.40 P.M.	37.4° C.	38° C.	38° C.	36.0° C.	35° C.	36° C.	37.0° C.	37° C.	37° C.	
Synthetic salt	200 mg.	June 19	37° C.	10.45	38.0° C.	38° C.	38° C.	37.5° C.	37° C.	37° C.	36.8° C.	37° C.	37° C.	37° C.

Conclusion. There is apparently no difference in the toxic and and irritant properties of synthetic and natural sodium salicylate in large doses. What the effects of the therapeutic doses administered to rabbits over a considerable period of time are is a question that can only be answered by a series of long and careful experiments, which we are now undertaking.

In experimenting with large doses the individual equation of the animal seems to count for more than the weight of the animal or the amount of the drug administered.

TEMPERATURE EXPERIMENTS. Here, again, rabbits differ from dogs in their behavior to the salicylates. Whereas dogs showed no drop in temperature, the curve in rabbits was irregular, from which it is difficult to deduce a rule.

SUBSEQUENT EXPERIMENTS—SUMMARY.

NATURAL SODIUM SALICYLATE.

Rabbit.	Date.	Injected, mg.	Symptoms.	Weight of rabbit approximately three pounds.
No. 1.	Oct. 9, 1915	200	4.30 P.M.	No symptoms.
	Oct. 14, 1915	300	3.25 P.M.	" "
	Oct. 15, 1915	400	4.25 P.M.	" "
	Oct. 15, 1915	500	11.10 A.M.	" "
	Oct. 15, 1915	600	4.30 P.M.	" "
	Oct. 16, 1915	700	11.20 A.M.	Slight symptoms of shock, with rapid recovery.
No. 2.	Oct. 15, 1915	600	2.30 P.M.	No symptoms.
2.	Oct. 15, 1915	700	4.00 P.M.	Slight symptoms of shock with rapid recovery.
3.	Oct. 18, 1915	800	4.55 P.M.	Died immediately after injection.
4.	Oct. 18, 1915	800	5.10 P.M.	Died immediately after injection.
5.	Oct. 18, 1915	400	5.20 P.M.	No symptoms.
5.	Oct. 20, 1915	600	10.40 A.M.	Incoördination for a few minutes; rapid recovery.

SYNTHETIC SODIUM SALICYLATE.

No. 1.	Oct. 9, 1915	200	4.20 P.M.	No symptoms.
1.	Oct. 14, 1915	300	3.20 P.M.	" "
1.	Oct. 14, 1915	400	4.30 P.M.	" "
1.	Oct. 15, 1915	500	11.15 A.M.	" "
No. 2.	Oct. 15, 1915	400	2.35 P.M.	No symptoms.
2.	Oct. 15, 1915	500	3.30 P.M.	" "
2.	Oct. 16, 1915	600	4.20 P.M.	" "
2.	Oct. 17, 1915	700	11.15 A.M.	" "
No. 3.	Oct. 16, 1915	800	2.45 P.M.	Died immediately after injection.
No. 4.	Oct. 16, 1915	800	3.00 P.M.	Died immediately after injection.

EXPERIMENTS IN DOGS.—Vinci has reported the results of experiments in dogs. He administered sodium salicylate subcutaneously in a few instances intravenously and by the stomach tube. He

noted collapse, with fairly quick recovery, attempts to vomit, and salivation. He used the synthetic acid of Bayer.

Collapse and salivation were the chief symptoms in our experiments with doses of 4 gms. in a dog weighing 8 kgs. The animal recovered. During convalescence there was weakness, also a dragging of the hind legs. The temperature did not fall.

Experiment, Fourth Series. September, 1915. Black, shorthaired mongrel, 8 kgs.; 11 A.M., subcutaneous injection of 4 gms. natural sodium salicylate in 20 c.c. saline solution. Injection very painful. Salivation: dragging of legs. Recovery. The motions of the dog were at first excited, then stupid, then like collapse.

Toxic Doses. There is virtually no difference between the natural and synthetic acids except a difference arising from the less irritant action of the former. It is better borne by the stomach, and this fact slightly affects the toxicity in human beings. In rabbits the fatal dose was found to be 900 mg. to the kilogram of body weight. Toxic effects in dogs were noted after 0.5 gm. to the kilogram. Fatal doses were not tried. According to Vinci the fatal dose in dogs is 0.2 to 0.5 gm. to the kilogram of body weight.

Fatal Cases. We have been unable to find the report of any case fatal after the natural acid. Most of the deaths recorded were caused by sodium salicylate, and presumably the commercial product.

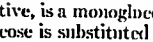
Comparative Clinical Effects. To make sure of obtaining a natural product through chemical changes in the living organism it is well to prescribe salicin. This glucoside is hydrolyzed in the organism, with the ultimate formation of salicylic acid, *e. g.:*

Salicin compares favorably with the synthetic salicylates. It has less action on the stomach and digestion. It was administered in 30 cases at the University and Bellevue Hospital Medical College and the Vanderbilt Clinic. The 5-grain tablets in use at these clinics are too small a dose. Twenty grains every four hours is the most satisfactory, but in these doses, as Dixneuf has pointed out, salicin must be carefully employed.

Acute Rheumatism. Saligenin, or salicyl alcohol, was used in 6 cases. Thirty grains were given three times a day. It is more powerful than salicin, is more effective, and in these doses produced noises in the ears and some salivation. It must be used with care.

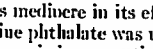
The reason for the powerful effects of saligenin may be that it has a phenol and an alcohol group arranged thus:

Salicin, which is less active, is a monoglucoside, a natural product of saligenin, in which glucose is substituted for the phenol nucleus, *e. g.*:



Phthalic Acid. It is stated by Juvalta that phthalic acid is oxidized into salicylic acid and phenol. Mosso, however, was unable to confirm this result. He apparently leaves it undetermined after experiments which he says are insufficient. Stockman has recently spoken of phthalic acid as mediocre in its effects.

Phthalic acid as cotarnine phthalate was used in 3 cases of acute rheumatism. Its action on pain is very satisfactory. Phthalic acid is decomposed completely in the human organism:



Sodium cinnamate was used in 60 cases by subcutaneous injection. The injections are very painful unless controlled by anodynes. It is effective if it can be given in large enough doses, but owing to its relatively slight solubility it is not easy to employ more than 1 gm. at a time.

Methyl salicylate, used locally, has an excellent, if passing, effect on the pain and swelling of acute rheumatism.

Factors in Cases of Poisoning. It was clearly shown by Mlle. Chopin, in her thesis, that sodium salicylate is more quickly excreted in children than in adults and more quickly in healthy adults than in nephritics. The inference is fairly obvious. Salicylic acid or sodium salicylate tends to be more toxic when the kidney is impaired. Other causes affecting toxicity, as we have noticed, are: (1) Alcoholism; in these cases the salicylates should be given with caution. (2) The state of the stomach. (3) Diseases of the alimentary tract affecting the oxidizing of the benzol nucleus all increase the toxic effect of the salicylates. (4) Salivary glands. Salivation is always the symptom that precedes collapse, though delirium may occur first. Flushing of the skin is an early symptom of poisoning, especially worth notice, if nose-bleed occurs, too. Deafness and noises in the ears are very early symptoms. Disorders of the sense color, in which things look greenish or greenish yellow, as patients describe their perceptions, are late signs often noted during convalescence. The musical sounds, wholly abnormal and very disquieting, are intermediate between the period of rising cerebral disorder and dangerous collapse.

An experience of several years shows that these symptoms are almost equally incidental to both acids when pure, though they occur less frequently after the acid prepared from oil of birch or

gaultheria. In this respect the opinions of Latham and of Stokvis hold good today.

Fatal cases are recorded by different authorities. Vinci describes one after 35 gms. of sodium salicylate, the largest dose ever taken at a time. Headache, delirium, salivation, and coma, ending in death, marked the course of poisoning, as they do in others. In nearly all instances a cumulative effect, first noticed by Dixneuf, is reported. Such cases are not infrequent; instances are described by Sée, Chopin, Georges Huber, Wattelet, Quincke, Petersen, Empis, Heffermann, Binz, Koelin, Léonhardi-Aster, Fürbringer, von Jaksch, Wittich, Bertaguini, and Buss.

Conclusions. 1. When pure samples, whether natural or synthetic, are used the effects in animals are virtually the same.

2. The difference between the natural and synthetic salicylates in men is somewhat more distinct. In the case of the natural acid when administered to adults there was less gastric disturbance, the cerebral effects were slighter, and in general it may be said that this substance is better borne than the commercial acid.

3. It is not so toxic in very large doses, though when more than 75 grains are given in twenty-four hours there is a tendency to delirium in the susceptible to salivation and flushing of the integument.

4. The noises in the ears are noticed on the second day, as a rule, of administration.

5. It seems clear that the natural acid has less cumulative effect.

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